“DOES OXYBUTYNIN DECREASE IRRITATIVE LOWER URINARY TRACT SYMPTOMS FOLLOWING TURP? – A PROSPECTIVE, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL”

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A dissertation submitted to The Dr. M.G.R. Medical University, Tamilnadu, in partial fulfillment of the requirements for M.Ch. Branch-IV (Genitourinary surgery) examination to be held in August 2009.

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Certificate

This is to certify that the work incorporated in this dissertation entitled "**DOES OXYBUTYNIN DECREASE IRRITATIVE LOWER URINARY TRACT SYMPTOMS FOLLOWING TURP?- A PROSPECTIVE,RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL**" is a bonafide work done by Dr. John Samuel Banerji in partial fulfillment of the rules and regulations of MCh Branch IV (Genitourinary Surgery) examination of the Tamil Nadu Dr. MGR Medical University, Chennai to be held in August 2009.

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CONTENTS

INTRODUCTION

Lower urinary tract symptoms (LUTS) due to benign prostatic enlargement (BPE) pose a significant impact on the quality of life of men around the world. Although modern medical therapies are the first choice in treating mild to moderate LUTS, surgical therapies remain the cornerstone in the treatment of BPE. Transurethral resection of the prostate (TURP) is the most common modality of surgical treatment for BPE, and has been the gold standard for the past few decades [1, 2]. Following TURP, a sizeable proportion of men have frequency and urgency that may continue for a few days to several weeks. In the immediate post operative period, bladder discomfort due to an indwelling urinary catheter is distressing; more so in patients who have undergone a transurethral procedure, without going into retention. It is not unusual to find patients complaining of an uncontrollable urge to void in the postoperative period because of catheter-related bladder irritation. Several modalities of treatment have been tried with various

degrees of success for managing this troublesome side effect. The incidence of residual symptoms after TURP has been reported to be 5-35% [3, 4]. In a

study by Seaman and Blaivas, approximately 15 to 20% of patients who undergo transurethral resection of the prostate for benign prostatic hyperplasia have persistent or recurrent voiding symptoms requiring further therapy. The most common cause of persistent symptoms is detrusor overactivity (DO) [5, 6].

Similar symptoms of painful micturition have been reported following laser vapourisation of the prostate, and this apparently lasts longer and is more common than with TURP. It has been reported to be about 26% in a review by Hoffmann et al [7]. Irritating symptoms such as frequency along with terminal dribbling and urgency are the most common complaints after catheter removal. We feel that the symptoms of frequency ,urgency and pain are worsened by the fact that there is a raw surface viz. the prostatic fossa that would cause irritation, and worsen such symptoms.

There has been a similar study by Iselin and Schmidlin [8], where the authors have used Oxybutynin for 5 days after TURP. They subsequently

evaluated symptoms using the Boyarsky score, and also performed urodynamic studies on the subjects. Based on this study we planned to evaluate the role of oxybutynin in alleviating post TURP lower urinary tract symptoms.

AIM OF THE STUDY

The aim of the study was to evaluate the symptomatic effect of oral 5 mg Oxybutynin extended release, in the control of irritating voiding symptoms after trans urethral resection of the prostate(TURP).

REVIEW OF LITERATURE

Despite the impressive results of medical therapy for LUTS due to BPE, reported reductions (45–60%) in the IPSS on a representative a-blocker such as tamsulosin are inferior to TURP (up to 80% reduction in IPSS). In addition, reported improvements in maximum urinary flow rate (Qmax) following treatment with tamsulosin (20–40%) are vastly inferior to those reported after TURP (80–90%). For these reasons, TURP is the preferred option for patients with severe LUTS or complications of BPE. Various studies quote coexisting bladder outlet obstruction combined with detrusor overactivity in 45% of the patients. Detrusor instability is common in men with evidence of outflow obstruction due to benign prostatic enlargement and typically reverses in about two thirds of patients after transurethral resection of the prostate (TURP).

Early incontinence may occur in up to 30–40% of patients; however, late iatrogenic stress incontinence occurs in less than 0.5% of patients. Early incontinence is usually urge symptomatic, either because of irritative symptoms such as fossa healing and associated UTI or detrusor instability

caused by long-lasting BPH [9]. Few data reveal the relationship of the applied electric energy and the irritative symptoms postoperatively. Nevertheless, the amount of energy should be minimized. A smooth fossa with minimal residual necrotic tissue guarantees better healing and thus reduces the risk of chronic infection and irritative symptoms.

Among patients discharged after TURP there is a considerable number of treatment-related symptoms in the first few weeks. In a study by Mogensen [10], 79.7% of patients who underwent TURP were incontinent due to urgency, to some degree.42% continued to have urgency for upto 4 weeks. Gormley et al [11] studied 12 males with a mean age of 80 years and performed urodynamic studies pre and post TURP. Postoperatively, although 8 became continent, they continued to have frequency and urgency after removal of the catheter. Preoperative urodynamic assessment of obstruction in the incontinent male with benign prostatic hypertrophy may be useful since the severity of incontinence responds well to TURP if there is marked obstruction.

Detrusor overactivity following TURP is frequently bothersome in the first few days after withdrawal of the bladder catheter. Various theories have been put forward for these symptoms. Surgical trauma and cauterization of the prostatic capsule possibly incites a local inflammatory reaction, which alters the activity of the neural afferents of the bladder base, leading to sensory urgency[8].

The tip of the transurethral catheter and its balloon may cause detrusor instability. In addition, perioperative bladder wall distension from the continuous irrigation may trigger short term tensile reactions in the detrusor smooth muscle. Changes in vascular perfusion of the bladder have also been implicated in triggering such responses. The latter was corroborated in a study by Mitterberger [12] et al, 50 subjects had persistent LUTS after TURP. These men were evaluated with quality of life scores, International Prostatic Symptom Score (IPSS), pressure flow studies and trans rectal Doppler ultrasound to assess the vascular resistance. When men with persistent storage symptoms (15 patients; group 1) were compared with those with no symptoms after TURP (35; group 2) there was a statistically

significantly higher RI of the bladder vessels in group 1, at 0.86 (0.068) than in group 2, at 0.68 (0.055) ($P < 0.001$).

LUTS is present after TURP, but this undergoes significant improvement as time passes. In a study from Taunton, MacDonagh [13] and colleagues evaluated two groups of 314 patients, with the European quality of life index, alongwith the Nottingham Health Profile. There was a significant improvement in all LUTS 6 weeks after TURP; post-micturition dribbling and storage symptoms continued to improve for up to one year.

In a study by Taylor et al, 71% patients had residual bothersome LUTS, the majority being urgency and urge incontinence [14]; several studies that suggest possibility of residual storage symptoms after TURP have been elucidated. Zhao et al [15] evaluated the changes of different urinary symptoms of patients with benign prostatic enlargement (BPE) after transurethral resection of the prostate (TURP) and its correlation with preoperative clinical parameters. Two hundred and eighty-one patients were followed-up immediately and 1 month after TURP, whose postoperative International Prostate Symptom Score (IPSS) and Quality of Life (QOL) score were compared with those preoperatively. Improvement of average

obstructive symptom score is greater than that of irritative symptom score. Among the seven symptoms, nocturia is the one with lowest improvement after TURP.

E. Mazaris et al divided prospectively and randomly 80 patients into 4 groups of 20 each, who underwent TURP. Group A was the control group, in group B tamsulosin 0.4mg OD, in group C tolterodine 4mg OD and in group D a combination of tamsulosin and tolterodine in the aforementioned doses, were administered after catheter removal.They concluded that the administration of tolterodine for LUTS after TURP helps reduce the incidence and severity of urgency and urge incontinence and offers a better quality of life.

O'Sullivan [16] and colleagues studied the effect of transurethral resection of prostate on quality of life (QOL) and urinary symptoms in patients with benign prostatic hyperplasia (BPH).They used four indices viz. the International Prostate Symptom Score , the Montgomery and Asberg Depression Rating Scale(MADRS), the McGill Pain Questionnaire(MPQ), and the QOL questionnaire Short Form-36. The MADRS score at 1 month (5.4) and 3 months (4.9) were lower than they were post-operatively (9.2).

The MPQ is a tool commonly used to evaluate acute and chronic pain. The sum of the rank values yields the pain-rating index and the greater the MPQ scores, the greater intensity of perceived pain. The MPQ scores were less at 3 months than they were post-operatively.

There have been reports of painful micturition following LASER ablation of the prostate. In a study with 80 patients, Lane et al [17] compared visual analogue scores in groups who underwent prostatectomy with the Holmium Laser and in the other who had KTP laser prostatectomy. The visual analogue scores in the Holmium group were significantly higher than the KTP group, and this persisted till 3 weeks.

Irrigation of the bladder after transurethral resection of the prostate is often distressing because of pain arising from detrusor muscle spasm. The effect of post-operative oral diazepam was compared by Nott et al. Effects of diazepam, sacral epidural (caudal) block at the time of surgery, both treatments together and a control group, were assessed by three-point rank scoring. Either treatment significantly reduced the incidence of pain reported by patients, $P < 0.001$. No patient experienced pain after both treatments[18]

Is it possible to predict which subgroup of patients, would continue to experience troublesome urgency and frequency after TURP? To answer that question, Kageyama [19] from Japan devised a novel study, in which they chose 14 subjects who had pre operative urodynamics alongwith single photon emission computed tomography (SPECT). They concluded that those patients who had decreased blood flow to the frontal cortex, as suggested by SPECT, were at increased risk of having persistent detrusor over activity in the post operative period. They also noticed that those with a bladder volume of less than 160 ml had increased risks of immediate postoperative symptoms.

There have been several other modalities in dealing with postoperative symptoms after TURP. Periprostatic nerve block at the time of TURP has been tried successfully by Gorur et al [20]. They included 40 male patients with benign prostatic hyperplasia who underwent TURP, and they were divided randomly into two groups. All patients were operated under general anesthesia. The study group of 20 patients received periprostatic bupivacaine (0.5% 20 ml) injection (group I), and the control group, also consisting of 20 subjects, received only saline (NaCl 0.9% 20 ml) injection (group II). All

injections were performed bilaterally into the periprostatic areas immediately after the TURP procedure via the transperineal route. In the postoperative period, all patients (groups I and II) received tramadol using a patient-controlled analgesia device. Postoperative pain was assessed and recorded using the visual analog scale (VAS) at postoperative hours 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, and 48. Total tramadol consumptions and additional analgesic requirements were also recorded and compared between groups. They concluded that periprostatic bupivacaine administration was a useful and safe method for postoperative pain control and reduced analgesic consumption in patients undergoing TURP.

Ricci and Minardi [21] evaluated patients who had undergone TURP and had sensory urgency. They used acupuncture reflexotherapy and compared it to placebo and oxybutynin, in patients who had urgency post TURP. 42 patients were randomly selected into three groups: 14 patients received placebo, 15 patients received oxybutynin, and 13 patients were treated with electrostimulation by acupuncture reflexotherapy. At the first check-up at 1 week, it was observed that the I-PSS and QoL scores were 12.6 +/- 4.3 and 3.8 +/- 1.3 in the group who received placebo; the scores decreased to 11.1

+/- 3.2 and to 3.1 +/- 1.0, respectively, in the 15 patients treated with oxybutynin and decreased to 6.1 +/- 2.6 and 1.3 +/- 1.1, respectively, in the 13 patients who underwent acupuncture reflexotherapy. The voiding diaries revealed that the average number of daytime voidings decreased by 8% in patients who received oxybutynin and decreased by 20% in 13 patients who underwent reflexotherapy; the average number of nocturnal micturitions decreased by approximately 20% and 60%, respectively, in patients who received oxybutynin and reflexotherapy.

In the paediatric age group, catheter related bladder spasms are common. Park et al [22], in a group of children who had undergone ureteral reimplantation, showed that with use of a nonsteroidal anti-inflammatory agent viz. Ketorolac, there was a significant decrease in bladder spasms. Agarwal et al [23] used a single dose of tolterodine 2 mg in patients who had undergone transurethral surgery, and assessed the discomfort in the immediate post op period in the recovery room. There was an absolute risk reduction in symptoms of 19%. The number needed to treat was 5.

Other anticholinergics like emepronium bromide (Cetiprin) have been used intravesically, and were found to be effective. The analgesic requirement in the group receiving Cetiprin was significantly lower [24].

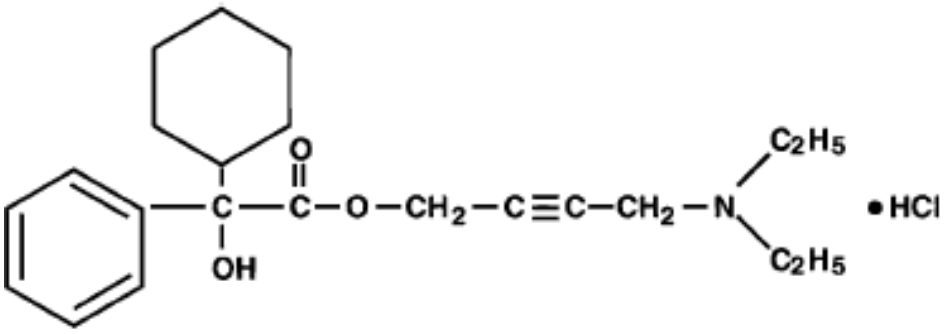
Muscarinic receptors

Five different receptor types (M1–M5) have been identified, that vary in distribution throughout the body, depending on the particular organ system. In the bladder the predominant receptors are the M2 and M3 subtypes. Although the M2 subtype is the most abundant receptor in the bladder, it seems that the M3 receptor subtype is most directly responsible for the effects on the bladder, because it mediates detrusor contractility.

Oxybutynin and mechanism of action

Oxybutynin chemically is 4-diethylaminobut-2-ynyl 2-cyclohexyl-2-hydroxy-2-phenylacetate with a formula of $C_{22}H_{31}NO_3$. It is a tertiary amine that exists commercially as a racemic mixture of R- and S-enantiomers (R-

OXY, S-OXY). The mechanism of action of oxybutynin is 2-fold, consisting of (1) its antimuscarinic properties; and (2) its spasmolytic action on detrusor smooth muscle cells [25, 26]. Oxybutynin exhibits stereoselectivity: R-OXY has greater anticholinergic activity compared with S-OXY. The spasmolytic effects on smooth muscle seem to be equal for the R- and S-isomers [27, 28]. In addition, oxybutynin resembles amines such as lidocaine and may have local anesthetic effects.



Chemical structure of oxybutynin

Studies from animal experiments have demonstrated that detrusor contractility occurs by M3 receptor-mediated smooth muscle contraction through hydrolysis of phosphatidylinositol and release of intracellular calcium. Furthermore, there is also evidence that M2 receptor-mediated contractions occur through inhibition of cyclic adenosine monophosphate-mediated relaxation of detrusor smooth muscle. As a result, by binding to the M2 and M3 muscarinic receptors of urothelial and detrusor smooth muscle cells, oxybutynin exerts its therapeutic effect by interrupting signal transduction pathways that cause detrusor contraction.

Oxybutynin binds to M3 muscarinic receptors on the detrusor muscle of the bladder, preventing acetylcholinergic activation and relaxation of the muscle.

Extended-release oxybutynin uses an osmotic system (OROS) to deliver a controlled amount of oxybutynin chloride into the gastrointestinal tract over a 24-hour period when taken once daily [29]. It resembles a conventional tablet but has a two-part core consisting of a drug layer and below it, a "push" layer containing osmotically active components, the whole surrounded by a semipermeable membrane with a laser-drilled opening in

the drug layer. Water in the gastrointestinal tract enters the tablet and mixes with the drug to form a suspension. The "push" layer expands and pushes the suspended drug out of the orifice and into the gastrointestinal tract for eventual absorption [30] Pharmacokinetic studies have indicated a slow rise in mean plasma concentration of the isomer R-oxybutynin for 4 to 6 hours after a single dose of OROS oxybutynin, followed by maintenance of steady concentrations for up to 24 hours, minimizing the fluctuations between peak and trough associated with TID dosing of 5-mg immediate-release oxybutynin tablets.

Oxybutynin metabolism

Oxybutynin is extensively metabolized by first-pass hepatic metabolism after administration of an oral immediate-release dose. The cytochrome P-450 (CYP) isoenzymes are the most abundant drug-metabolizing cytochromes in the liver and small intestine, mediating phase I drug metabolism through oxidation, reduction, and hydrolysis. CYP-3A4 is a specific cytochrome that converts oxybutynin to its active metabolite, N-

desethyloxybutynin (N-DEO). As a result, bioavailability after oral dosing of

oxybutynin is only 6%, with levels of N-DEO reaching peak plasma concentrations that are 4 to 10 times greater than the native compound. Because of the high affinity of N-DEO for muscarinic receptors, particularly in the parotid gland, it is generally accepted that many of the anticholinergic adverse effects observed after oral dosing of oxybutynin are secondary to high circulating levels of its active metabolite, N-DEO.Oxybutynin was rapidly absorbed, maximum plasma concentrations (8 ng.ml-1) being reached in less than 1 h. The absolute systemic availability averages 6% and the tablet and solution forms display similar relative systemic availability. Plasma concentrations of oxybutynin fall biexponentially, the elimination half-life being about 2 h. Oxybutynin chloride has a long history of safety and efficacy dating back to the mid-1960s, when it was originally approved for the management of detrusor hyper-reflexia secondary to neurogenic bladder dysfunction. Originally developed by Majewski, oxybutynin was patented in1965. Oxybutynin has both musculotropic relaxant activity and local anesthetic activity, and has been one of the most extensively studied

agents in this pharmacologic group Early studies of the drug using cystometrography in patients who had neurogenic bladders and upper motor

neuron disorders proved the drug effective in controlling urinary urgency, frequency, and incontinence. The US Food and Drug Administration (FDA) eventually approved oxybutynin in 1975 for the treatment of uninhibited and reflex neurogenic bladders and for the treatment of enuresis in patients older than 5 years. In the early 1980s, oxybutynin was found efficacious not only for those who had neuropathic disturbances but also for patients who had detrusor overactivity without known neuropathic disturbance. In 1980, Moisey and colleagues reported the results of a randomized double-blind study in 30 patients who had detrusor instability. Their findings suggested that the drug provided subjective improvement of symptoms in most of the patients treated, with urodynamic improvement in half of the patients completing the study. This study and others allowed oxybutynin to gain FDA approval for its use in detrusor instability in 1992. Over the last few decades, oxybutynin has demonstrated efficacy and safety in several clinical trials

Safety and tolerability

The use of oxybutynin since the early 1960s has afforded clinicians the ability to thoroughly evaluate its safety and efficacy. One of the early clinical trials of oxybutynin evaluated it as therapy for irritable bowel syndrome and established its most common adverse events, namely, constipation, dry mouth, and visual disturbances. In a trial where efficacy of extended release agents for overactive bladder were studied,

A secondary goal of the trial was to evaluate tolerability of extended-release oxybutynin by patient-reported adverse events. In this study, most adverse events were those that would normally be expected in patients treated with anticholinergic agents. Dry mouth was reported in 28.1% of patients, with other side effects being headache (8.1%), constipation (7.0%), and dyspepsia (5.9%). Extended-release oxybutynin was well tolerated in the OPERA (overactive bladder-performance of extended release agents) study, with total dry mouth being the most common adverse event (29.7%), which was statistically different (P = 0.05) from those taking long-acting tolterodine

(22.3%). Both groups showed a similar rate of discontinuation of therapy due to adverse events (*w*5% for each group). Other adverse events noted in

the study were mild or moderate dry mouth, diarrhea, constipation, headache, and urinary tract infection. In a recent trial, extended-release oxybutynin was evaluated over up to a 12-month period to study the long-term safety profile. This multicenter trial followed a total of 904 women and 163 men using quality-of-life assessments to measure the impact of incontinence and evaluate treatment outcome with extended-release oxybutynin. In this study, most discontinuations were in the first 3 months (25.5%) and were related to adverse events, most commonly dry mouth (8.4%). Of those continuing after 3 months, 62% remained on extended-release oxybutynin for 1 year. Patients had significant improvements in quality of- life measures in this multicenter trial [31].

Because oxybutynin and its extended-release form are tertiary amines, they can theoretically cross the blood-brain barrier and produce central nervous system adverse events. Central nervous system adverse events of oxybutynin, including somnolence, dizziness, and insomnia, were limited in the OPERA study and were similar to tolterodine. The incidence of central

nervous system adverse events was reported at rates between 1.2% and 4.3% for extended-release oxybutynin and between 1.1% and 5.2% for extended-

release tolterodine over the entire study period. These adverse events led to early discontinuation by only 1.5% of the participants taking extended-release oxybutynin and 0.5% of participants taking extended-release tolterodine. This difference was not statistically significant [32].

Why oxybutynin?

Bladder discomfort related to an indwelling catheter can exacerbate postoperative pain. It mimics overactive bladder syndrome that is resistant to conventional opioid therapy. Muscarinic receptor antagonists are effective for treatment of the overactive bladder.

Although a single study in the late seventies by Wein [33] and co workers showed no benefit with 10 or 20 mg oxybutynin in relieving bladder spasms, there have been many subsequent reports to the contrary.

Tauzin-Fin P [34] et al used sublingual oxybutynin in patients who underwent radical prostatectomy, and were on a catheter. Oxybutynin 5mg was given 8 hourly for 24 hours to one group, along with placebo to the control. A 16F Foley catheter was placed during the vesico-urethral

anastomosis and the balloon inflated with 10 ml of saline. Pain was assessed in the recovery room starting 10 min after extubation using a 100-point

visual analogue scale (VAS). The patients were asked to specify whether pain was related to the surgical incision or bladder pain. Standardized postoperative analgesia included acetaminophen and tramadol administered via a patient-controlled analgesia system. They concluded that sublingual oxybutynin was an effective treatment for postoperative pain after radical retropubic prostatectomy and produces a significant reduction in tramadol requirements.

Kirkali and Whitaker [35] administered oxybutynin to 216 patients with LUTS or with a catheter in situ. Good results were obtained in 66% of patients who had no previous treatment and in 46% of patients who had taken various drugs before. It was just as effective in all age groups. Twenty-three per cent of patients experienced side effects and 10% were unable to tolerate the drug. They concluded that oxybutynin was an effective drug in the treatment of unstable bladder catheter-induced spasms.

Oxybutynin chloride and placebo were randomized in a double-blind trial to determine the effectiveness of the test agent in controlling post-transurethral

pain and spasm [36]. Oxybutynin chloride was found effective in controlling pain and spasm; no significant side effects were noted.

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In animal studies, oxybutynin chloride was found to exert a moderate anticholinergic effect on rabbit detrusor in vitro, which is reversible and competitive in nature and midway in potency between atropine and papaverine [37]. In addition, oxybutynin strongly antagonizes BaCl2-induced spasms of detrusor with a potency equivalent to that of papaverine and 10 times that of atropine. This musculotropic spasmolytic effect is slightly greater in rabbit than human or monkey tissue. This direct relaxant effect, unlike that of papaverine, is not mediated by the inhibition of tissue phosphodiesterase, but probably reflects oxybutynin's local anesthetic properties and associated effects on Ca++ fluxes and binding.

Oxybutynin chloride, a tertiary amine possessing anticholinergic and papaverine-like, direct muscular antispasmodic effects, has been used in controlled clinical studies in patients with neurovesical dysfunction, upper motor neuron bladders, enuresis, and primary muscle spasm. The cystometrically documented, synergistic, anticholinergic, and muscle relaxant activity of oxybutynin observed in these studies indicates that the

drug can be highly effective in the management of reflex neurovesical dysfunction, enuresis, and bladder spasm. [38]. Oxybutynin is widely used in patients who have neurogenic bladder dysfunction. Bennett and

colleagues [39] evaluated the efficacy and safety of high-dose oxybutynin chloride in patients who had multiple sclerosis, spinal cord injury, and Parkinson's disease. This trial was a prospective, 12-week dose-titration trial of extended-release oxybutynin. Doses were increased by 5 mg at weekly intervals to a maximum dose of 30 mg daily. Patient perception of efficacy versus side effects directed dose escalation. Of 39 patients enrolled in the study, 22 had multiple sclerosis, 10 had spinal cord injury, and 7 had Parkinon's disease. Within 1 week of treatment, over half of the patients reported a decrease in the number of voids per day, and at the end of the study, there was a statistically significant decrease in 24-hour voids, episodes of nocturia, and incontinence episodes. Most (74.4%) patients in this study requested higher doses (15 mg or greater) of extended-release oxybutynin, and therefore, these investigators concluded that in this population, doses of up to 30 mg may be more effective.

Oxybutynin has also been used in the intravesical form; in children with neurogenic bladders Adjunctive intravesical oxybutynin therapy increased

mean maximum bladder capacity and decreased bladder pressure in children with neurogenic bladder [40].

However, identified studies offered a low level of evidence, with most being poorly reported retrospective case series with potential biases. Although the incidence of side effects was lower with the intravesical route, side effects are still possible. To improve patient compliance and tolerability, alternative delivery systems for oxybutynin have subsequently been developed and include a once-daily formulation and a transdermal system. Oxybutynin chloride has been reported to be equally effective when given intravesically, transdermally, or in intrarectal form. Saito and colleagues [41] reported their 3-year experience of using a modified intravesical form (oxybutynin chloride with hydroxypropylcellulose) in patients who had neurogenic overactive bladder and were not satisfied with the oral form of the drug or other therapies. Cystometrography was used to evaluate patients before treatment, at 1 week, and at 3 years after the initial intravesical treatment. This study was limited to six patients whose mean bladder capacity before treatment was 129.7 mL. Cystometrography studies revealed that bladder

capacity increased to 283.5 mL and 286.8 mL at 1 week and 3 years post-treatment, respectively.

Transdermal forms of oxybutynin chloride are available and deliver the drug over a 3- to 4-day period after application to intact skin. Dmochowski and

colleagues [42] evaluated transdermal oxybutynin and randomized 520 adult patients to receive 1.3, 2.6, or 3.9 mg daily. Voiding diaries and incontinence-specific quality of life were part of the evaluation. In this study, the highest dose (3.9 mg) was associated with a significant reduction in the number of weekly incontinence episodes and daily urinary frequency, significantly increased mean voided volume, and improved quality of life. Using 2.6 mg increased mean voided volume. In a second large, randomized, double-blind trial, efficacy of 3.9-mg oxybutynin administered transdermally was compared with placebo. Oxybutynin significantly decreased the number of incontinent episodes per week compared with placebo (P ¼ 0.0165). In addition, the transdermal form reduced micturition frequency and increased voided volumes. Side effects of the transdermal form were mainly related to the site of application. Dry mouth and other adverse events associated with the oral form and other anticholinergics were

less common in transdermal oxybutynin [43]. Few studies have evaluated intrarectal administration of oxybutynin. In another study, patients not tolerating oral oxybutynin were offered an intrarectal form of oxybutynin. Fifteen patients who consented to the study were given 5 mg of intrarectal oxybutynin chloride twice daily.

After switching to the intrarectal route of administration, none of the patients chose to discontinue the treatment. All patients reported an improvement in their symptoms of overactivity, with 25% of patients claiming their symptoms had completely disappeared. Only 13.3% of patients reported mild-intensity dry mouth [44]. Although oxybutynin chloride has been studied in many routes of administration, the oral route is the most thoroughly evaluated and commonly used form. The enteral route of administration should be attempted first in most patients. Patients not tolerating oral oxybutynin can be tried on another form.

Despite the amply demonstrated efficacy and safety of antimuscarinic medications in appropriately selected female and male populations with symptoms of OAB some experts have expressed concern over the potential

effects of these agents on peak flow rate and PVR volume in male patients with LUTS associated with BPE.

However, the fear of retention is ill founded. Chapple and Roehrborn [45] emphasised that male OAB symptoms are storage LUTS that may coexist with bladder prostatic hyperplasia (BPH),bladder prostatic

enlargement (BPE), or BOO without being caused by the prostatic condition. The safety of the use of antimuscarinic drugs can be explained by the fact that these drugs act mainly by decreasing the urge and increasing bladder capacity during the filling phase, when there is no activity in the parasympathetic nerves releasing acetylcholine.

Hence, it can be hypothesised that the drugs block the afferent nerves initiating the micturition reflex, triggered by a tonic release of acetylcholine from nerves or, perhaps, from the urothelium.

Moreover, being competitive antagonists, the action of these drugs can be reduced during the voiding phase, when there is a massive release of acetylcholine. Hence, this may be the reason why the currently used dosages of antimuscarinic drugs do not lead to urinary retention.

MATERIALS AND METHODS

The study was carried out in the department of urology of the Christian Medical College.

Inclusion criteria

All patients undergoing TURP were included for the study

Exclusion criteria

1) Carcinoma prostate

2) Underlying neurological disease

3) Vesical calculus

4) Bladder diverticulum

Study type

Randomized, double blind, placebo controlled trial.

Method of randomization

Block randomization method was used for this study. They were stratified into blocks of 10 subjects each.

A pilot study was initially performed and 20 subjects who had undergone TURP were assessed for presence of irritative symptoms. 13 patients had severe symptoms after TURP. Of these, 7 were given oxybutynin and 6 were not. The frequency and urgency in all 7 were less than in those who did not receive oxybutynin. With this background, and the previous study viz. Iselin/Schmidlin's, using oxybutynin, it was assumed that there would be a difference of 38% in the treatment and placebo arm (84% in treatment arm and 46% in placebo, according to Iselin's study).

Sample size calculation

Power of study	90%
Alpha error	5%

Detection of 84% in treatment response, and 46% in placebo, with a power of 90% and 5% level of significance(2 sided) the sample size for each group was 40 per group.

Patients who were eligible, were consented in their own language prior to inclusion in the study.

All patients had a preoperative self assessment IPSS score(International Prostate Symptom Score).

TURP was carried out using monopolar cutting loop electrode, with Iglesias continuous flow resectoscope. There was a varied cadre of surgeons who performed the TURP's.

The patients were then randomized to receive 5 identical tablets of oxybutynin 5mg XL or placebo. The packaging of the drug and the placebo was done by the pharmacy department of the institution, according to the random code generated. The

packets were opaque, white and were numbered serially. The drug was dispensed by a nurse, who had no information about the contents of the packet, or the patient receiving it. Neither the investigator nor the patient knew which medication was being given to him.

Patients were instructed to take 1 tablet at bedtime for the following 5 consecutive days, beginning the day after surgery.

Catheters were removed on the 3rd post operative day, in the morning. IPSS score, visual analogue score, frequency of micturition,

nocturia,bladder diaries were monitored for the 1st, 3rd and 5th post op days; post void residue was recorded on the 3th post operative day. Side effects, if any were recorded.

Statistical analysis

Mean and standard deviation of IPSS scores, visual analogue scores, frequency , nocturia and post void residue were

calculated. Differences in day 3 and day 5 from baseline were computed to test for statistical significance. SPSS package 16.0 was used for computing the statistical analysis.

Name _____

Date _____

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1. Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5
2. Frequency Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5
3. Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Urgency Over the past month, how difficult have you found it to postpone urination?	0	1	2	3	4	5
5. Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5

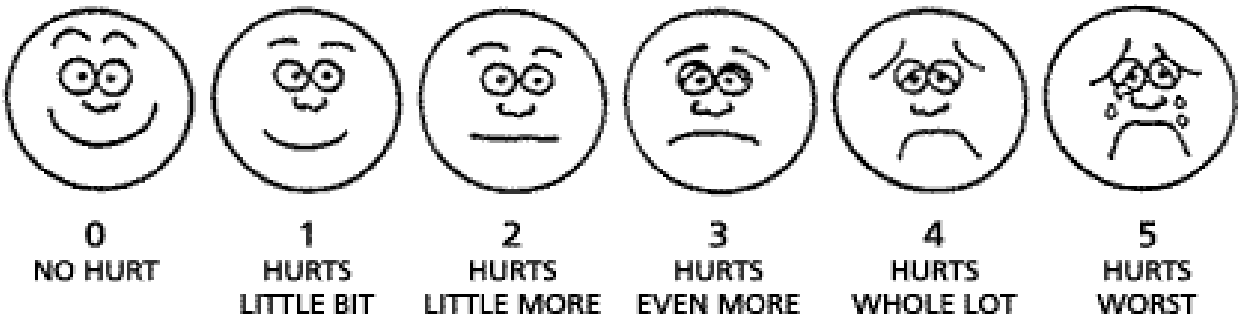
	None	1 time	2 times	3 times	4 times	5 times or more
7. Nocturia Over the past month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5

Total IPSS score ☐

0–7 = mildly symptomatic; 8–19 = moderately symptomatic; 20–35 = severely symptomatic

The IPSS score

The visual analogue score



The Wong Baker face scale was used for assessing pain and discomfort after the TURP. This is used as a measurement that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured.

All patients were administered this pain scale and these were then computed along with the IPSS, bladder diary and post void residue.

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RESULTS

There were 70 subjects who were enrolled. However 20 patients of the 70 failed to complete their bladder diaries, and were excluded from the analysis. Hence the analysis was undertaken for 50 subjects only.

The mean age in both the groups were evenly matched, as were all other parameters viz. IPSS, visual analogue score, frequency of micturition, nocturia , fluid intake, post void residues, and gland size.

Variables	Oxybutynin	Placebo
	Mean±SD	**Mean**±SD
Age	66.46±8.25	65.21±6.55
International Prostate Symptom Score		
Baseline	27.42±3.74	28.12±3.35
Day1	26.19±3.89	26.37±3.37
Day3	25.04±3.84	25.21±3.02
Day5	23.88±3.83	24.67±3.21
Visual Analog Scale		
Day1	4.27±0.67	4.17±0.76
Day3	2.62±0.75	2.83±0.82
Day5	2.00±0.98	2.04±1.08
Frequency of Urination		
Day1	9.92±1.49	9.79±1.91
Day3	7.81±1.92	8.29±2.07
Day5	7.35±1.96	7.78±1.88
Nocturia		
Day1	1.42±0.58	1.62±0.58
Day3	1.23±0.59	1.21±0.41
Day5	0.92±0.69	1.08±0.72
Fluid Intake(ml)	2913.46±523.12	2858.33±507.39
PVR(ml)	30.46±11.78	33.71±20.21
Gland size in gm	31.73±9.59	29.17±11.76

Descriptive statistics

IPSS trends over 1st, 3rd and 5th day

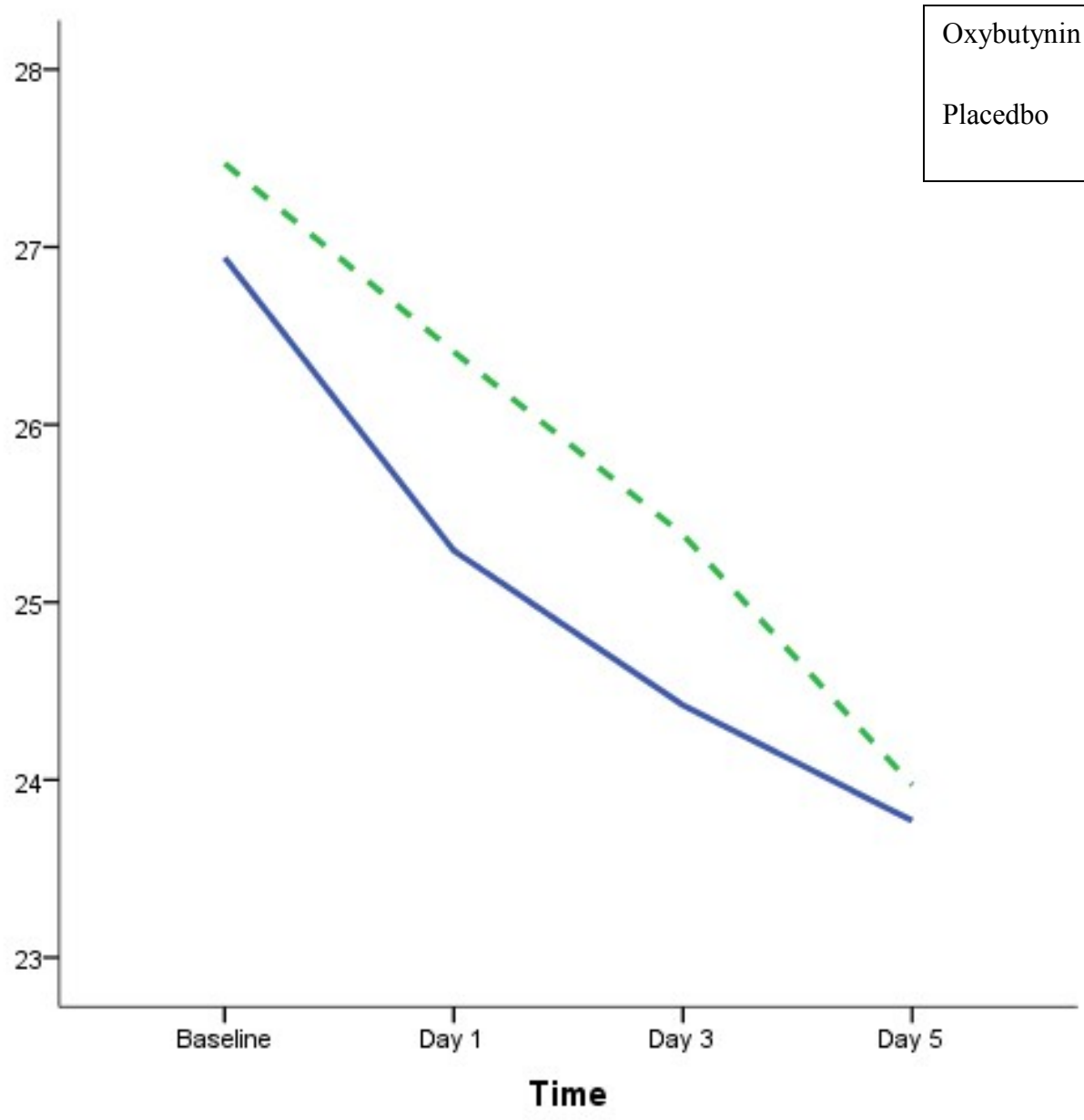


Fig. 1

Analysing the IPSS trends over the 1st, 3rd and 5th day, showed a decreased score in both the drug and the placebo arms. However, the difference in mean IPSS scores were most at the 3rd day, and this begun to plateau by the 5th day (Fig 1)

The histogram below shows that the frequency of change in IPSS scores followed a normal distribution curve, with an overall mean change of 3.5 points, with a S.D. of 2.188

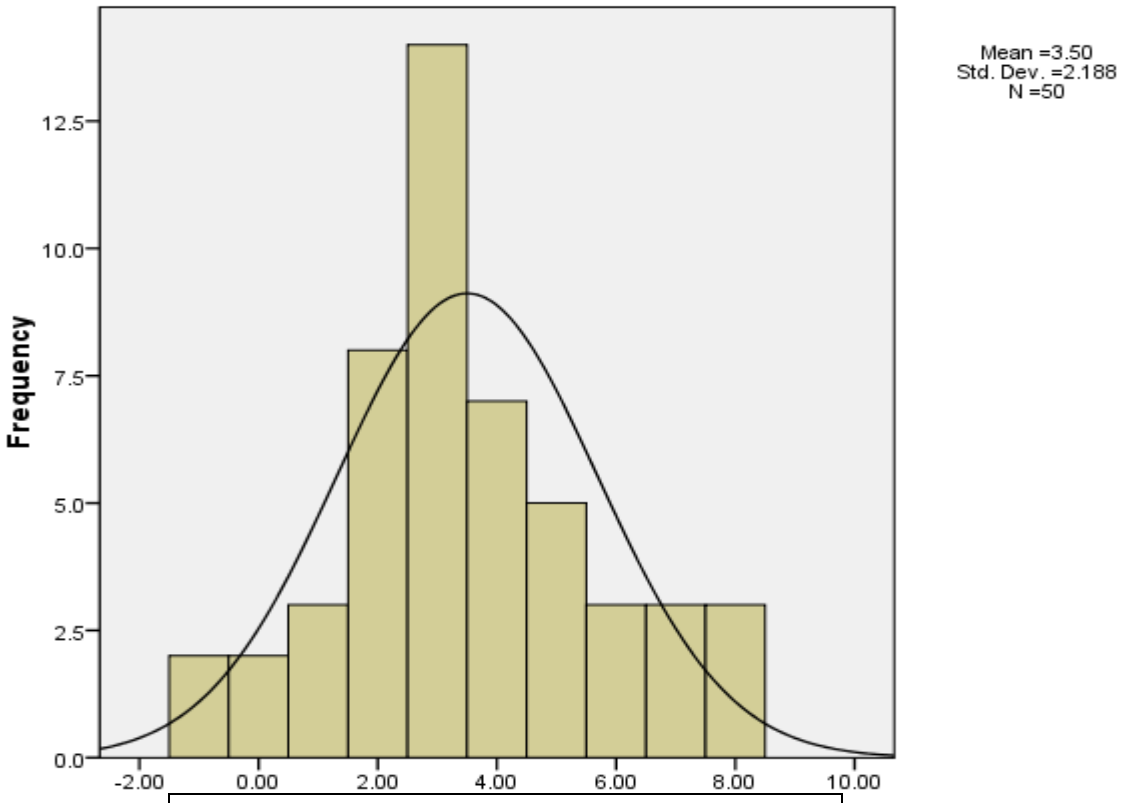
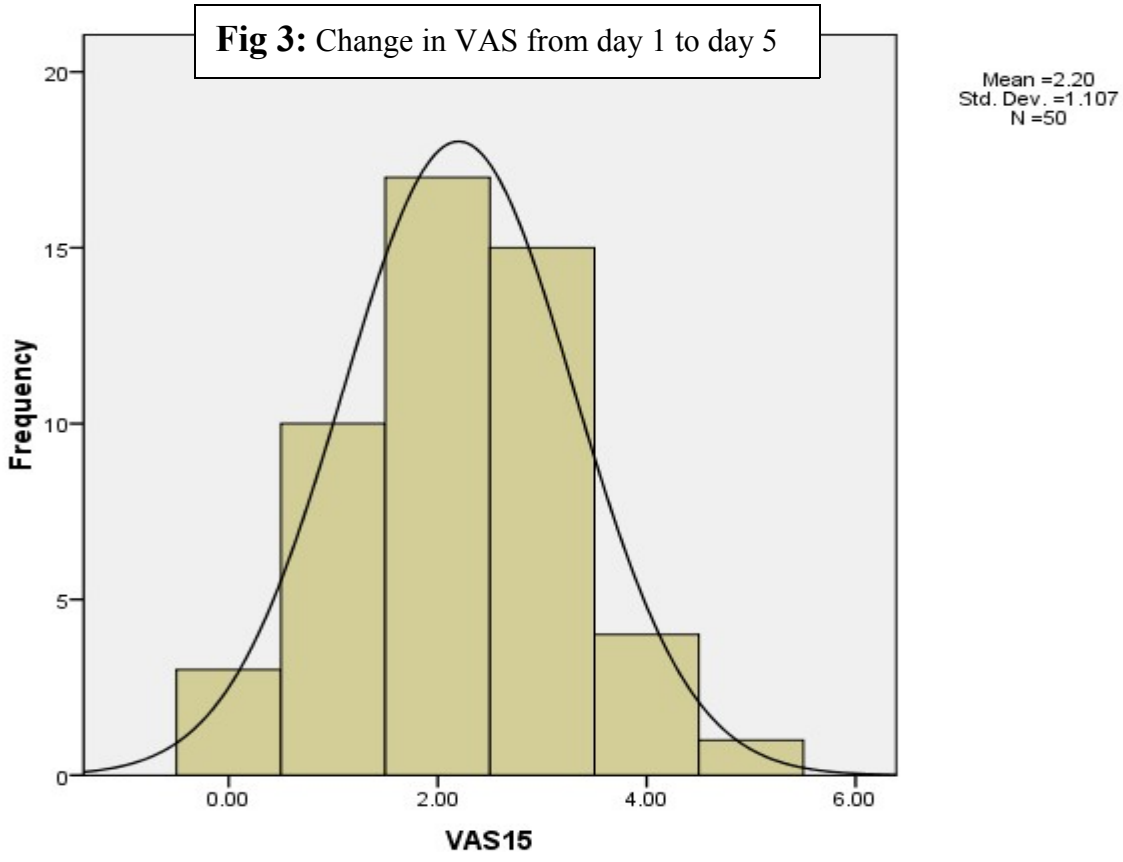
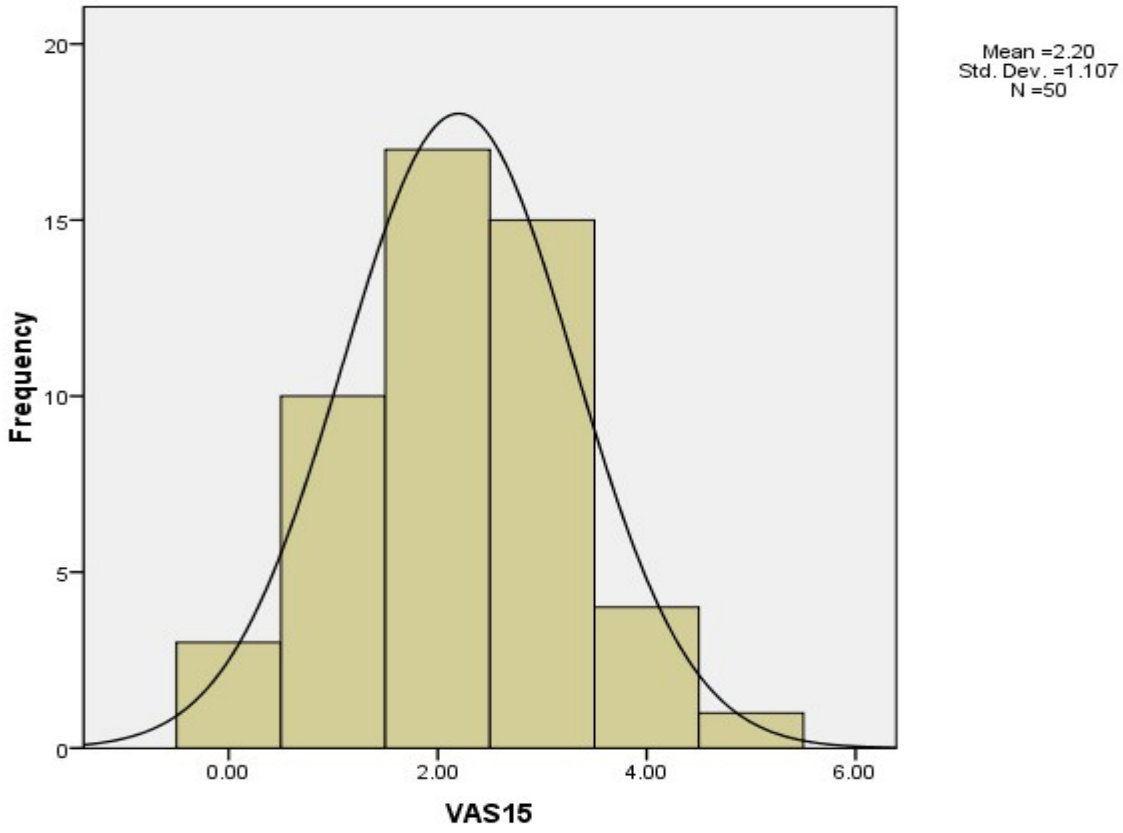


Fig. 2: IPSS change from day 1 to day 5

VAS:

Fig 3: Change in VAS from day 1 to day 5





The above histogram (Fig 3) shows a Gaussian distribution of the subjects who had change in the VAS .The overall mean change was 2.2 points on a scale of 6, and the S.D was 1.107.

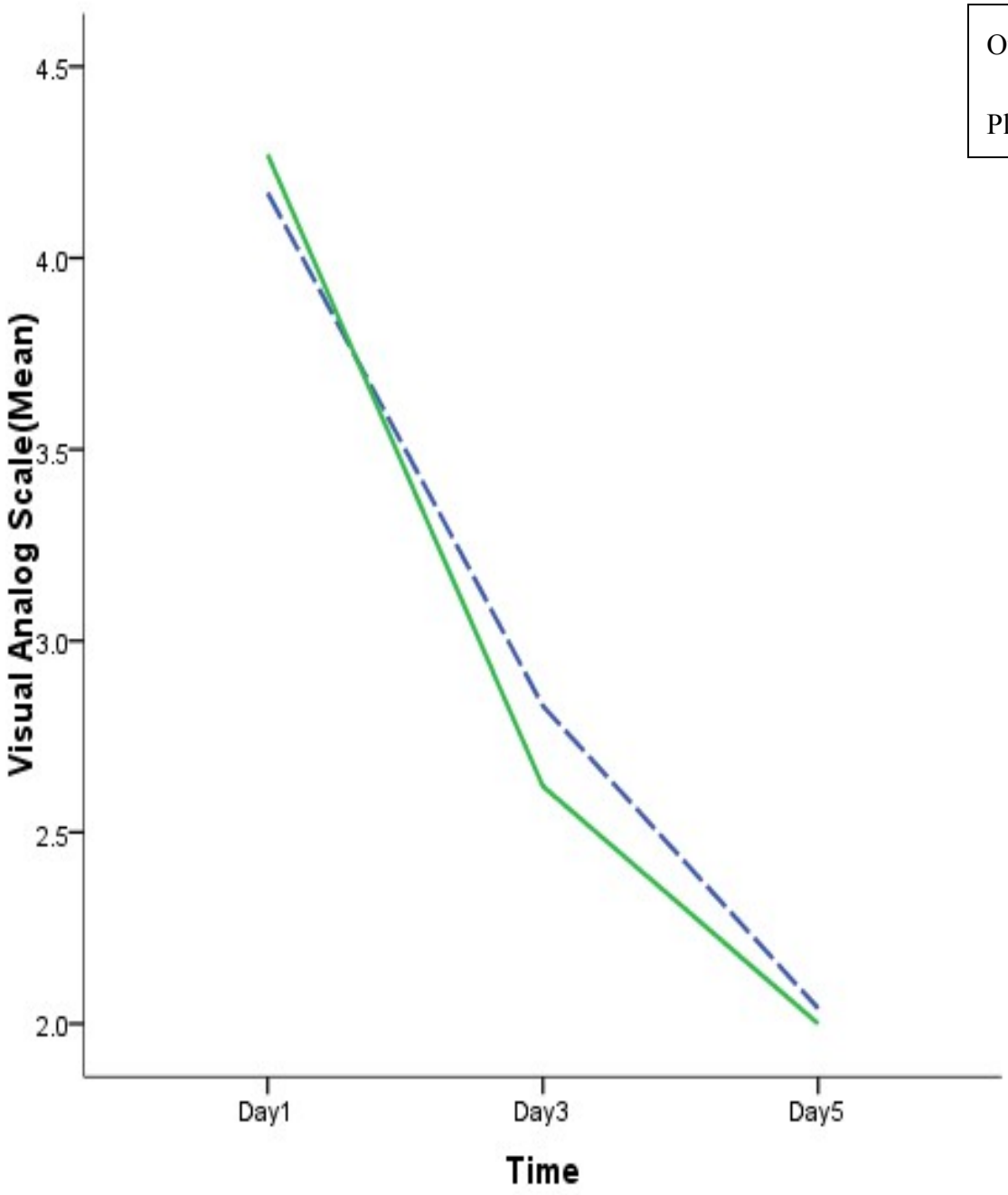

Oybutynin
Placebo
4.5
4.0
3.5
3.0
2.5
2.0
Visual Analog Scale(Mean)
Day1
Day3
Day5
Time

Fig. 4

The mean VAS (Fig 4) in the oxybutynin group was lower than the control group, but this was also more marked on the 3rd day(2.5 as compared to 3 in the placebo group). By the 5th day , the mean VAS scores of both groups had reduced.

Frequency of micturition:

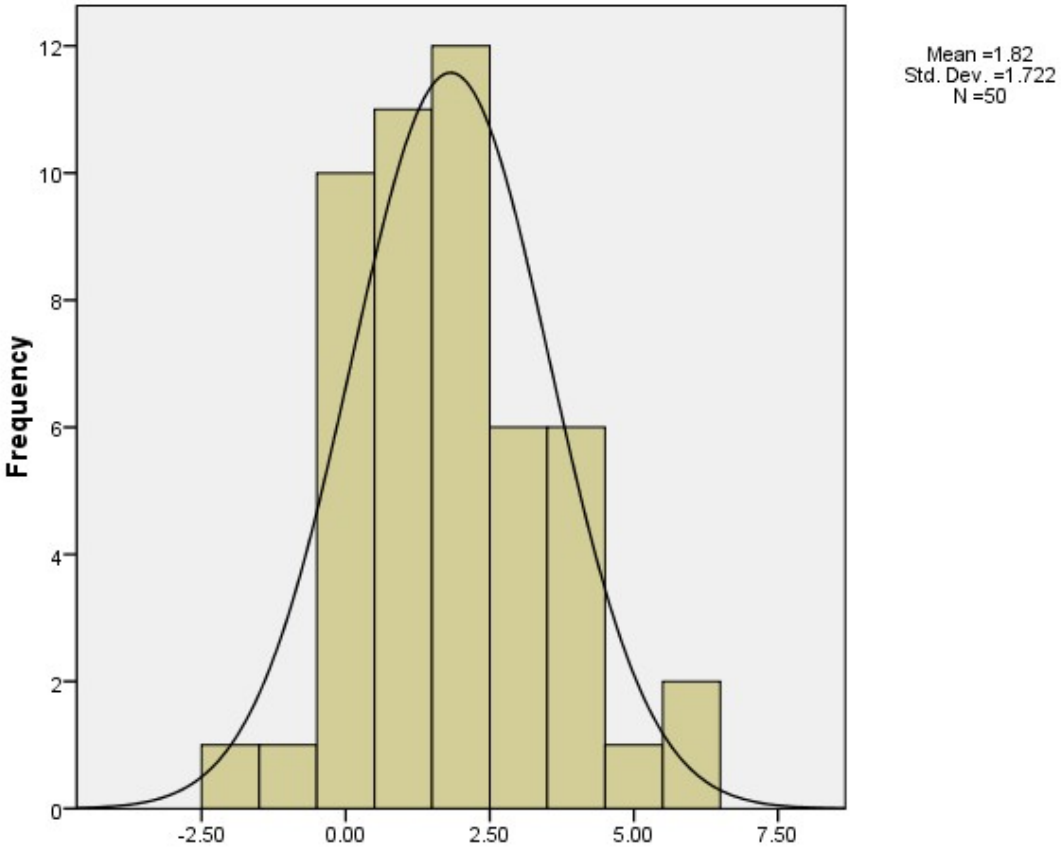
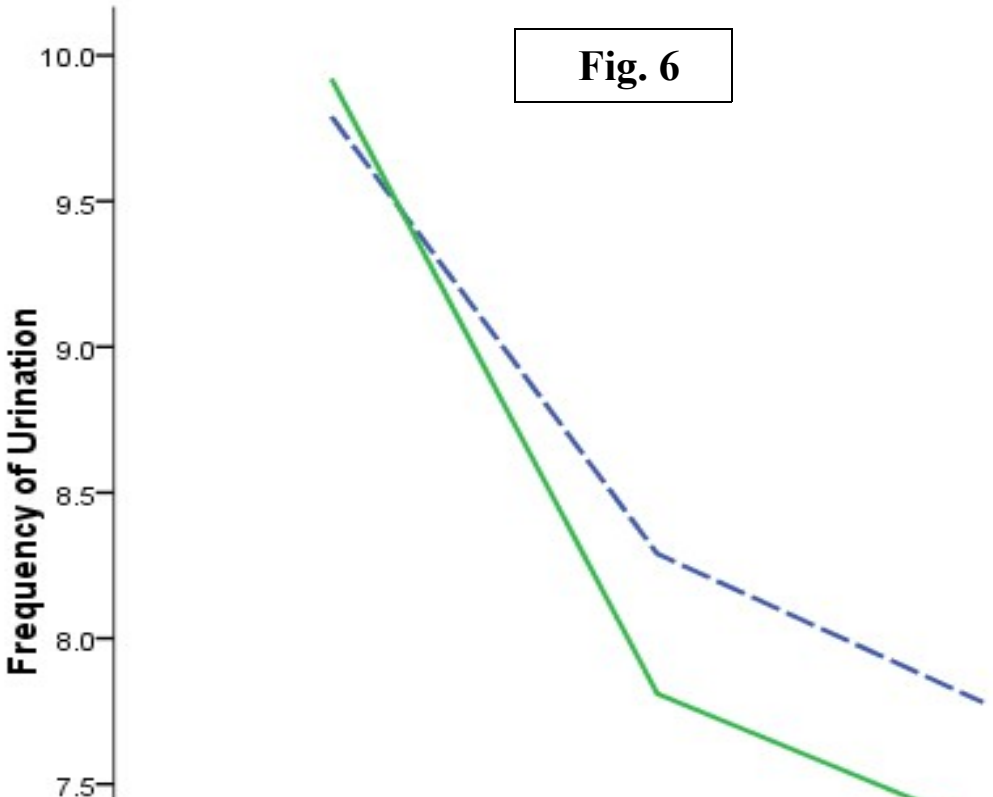
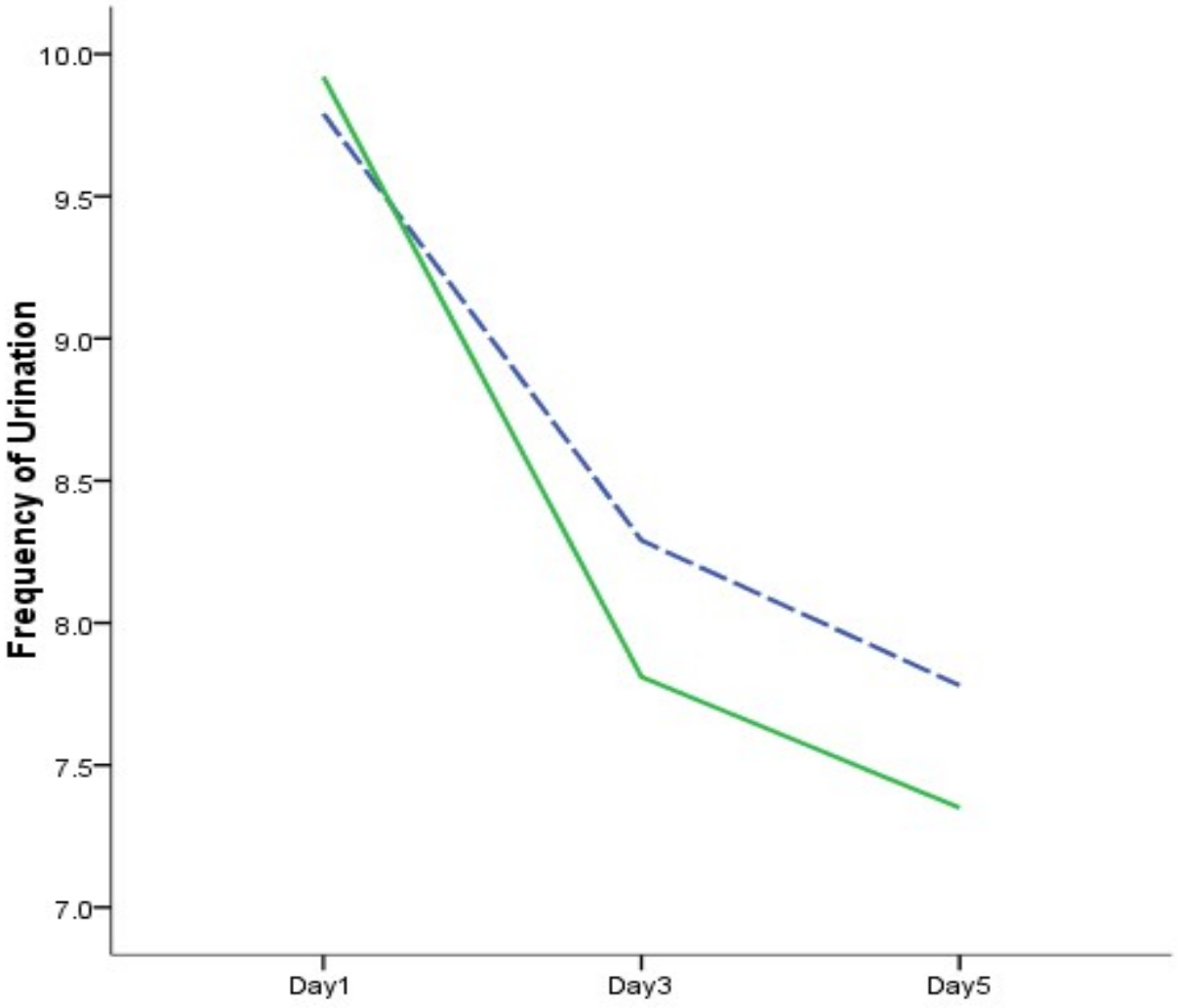


Fig 5: Change of frequency of micturition from day 1 to day 5

Fig. 6





Analysing the change in frequency of micturition, there was an appreciable change in the frequency , in the oxybutynin group(Fig 6) . This became more pronounced as the 5th day approached, and although there was a

decrease in the control group also, the difference in overall change was 18%. This was probably significant at 7% error.

Nocturia:

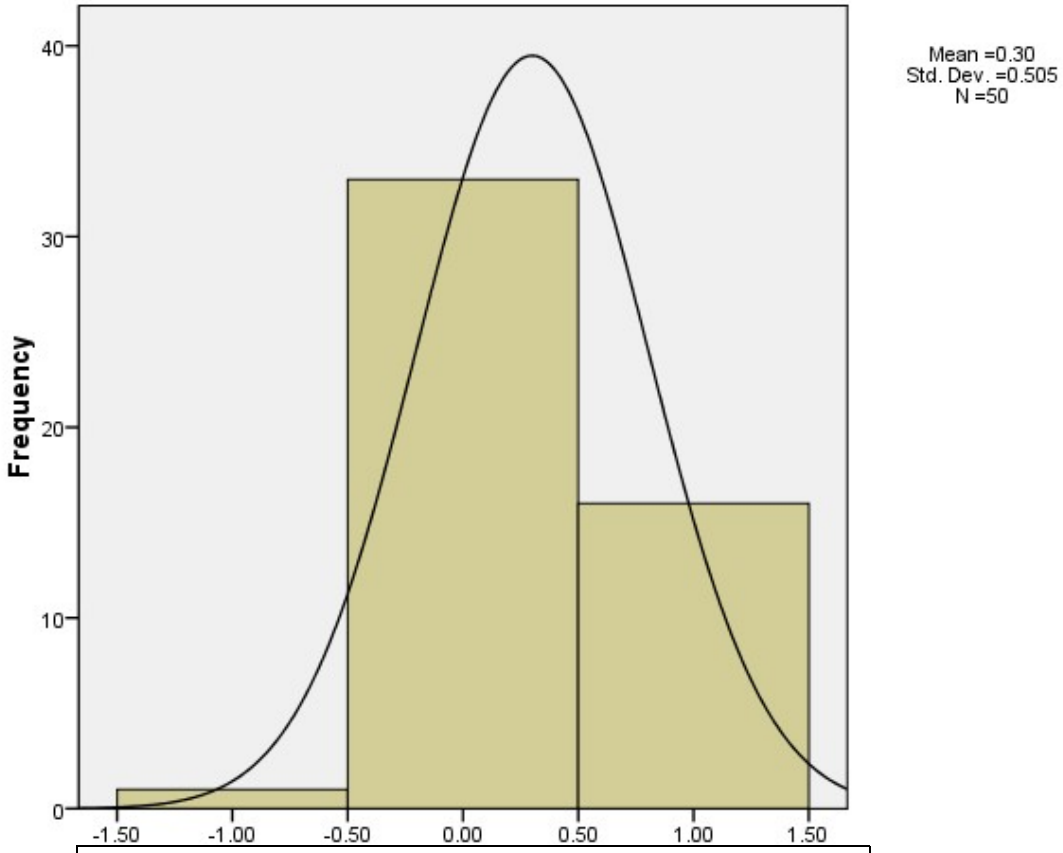


Fig 7: Change in Nocturia episodes from day 1 to day 5

The above histogram (Fig 7)shows the mean change in nocturia episodes from day 1 to day 5. The overall mean change was 0.30 and the S.D was 0.505.

Oxybutynin ____

Placebo -----

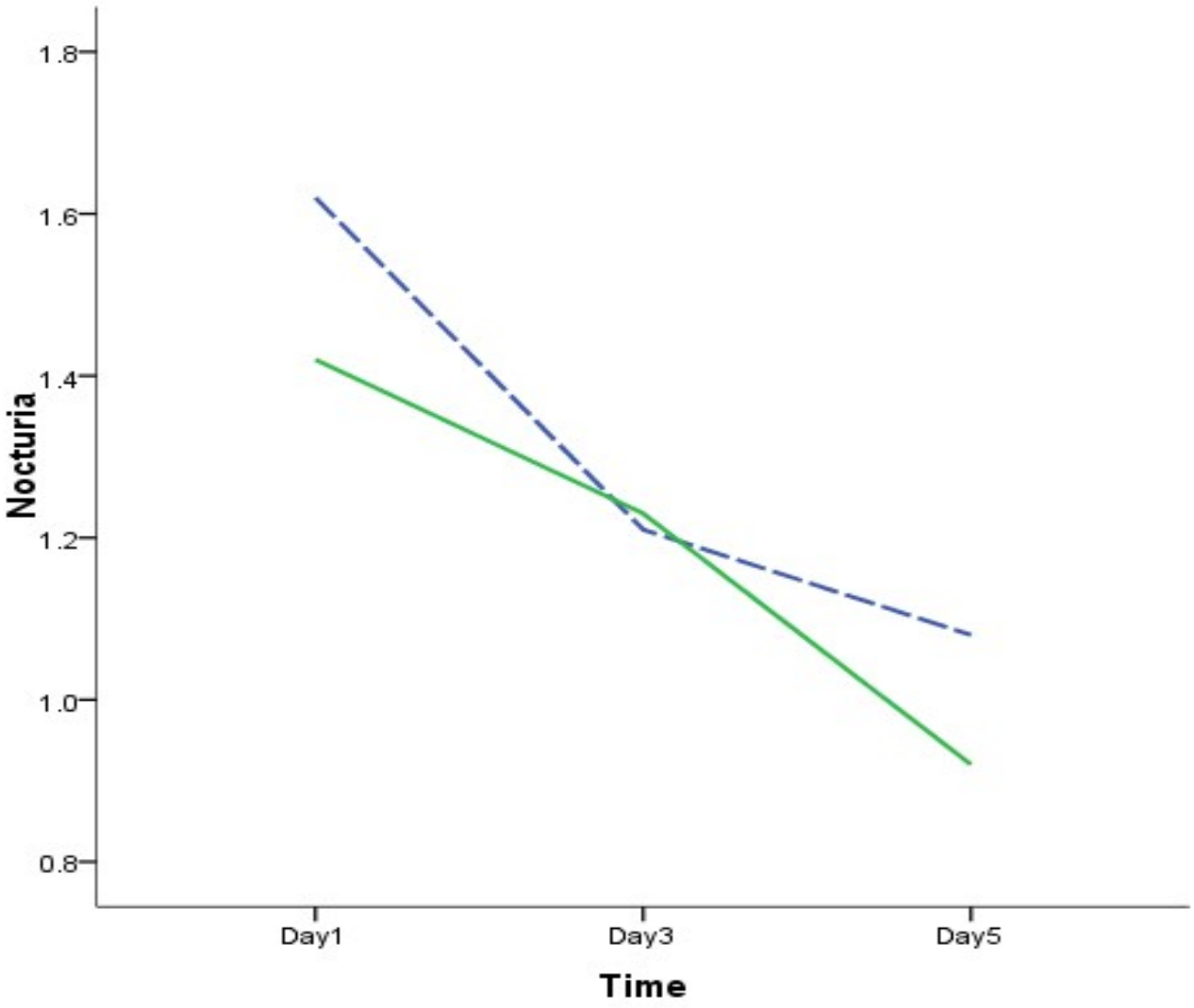


Fig 8

Nocturia was again less in episodes, especially on the 5th day(Fig 8) , where the graph shows a difference of nocturia episodes from 1.1 nocturia episodes

in the placebo group as compared to 0.9 in the drug group. Though the difference is small and not statistically significant, there is indeed a difference in the values which become pronounced at the 5th day.

Consolidated efficacy analysis

Efficacy analysis for IPSS

Variable	Oxybutynin Mean±SD	Placebo Mean±SD	Mean Difference	p value
IPSS Change from Baseline to Day1	1.75±1.32	1.23±1.50	0.519	0.203
IPSS Change from Baseline to Day3	2.91±1.76	2.38±2.19	0.532	0.352
IPSS Change from Baseline to Day5	3.53±2.40	3.45±1.98	0.801	0.899

Efficacy analysis for Visual analogue score

Variable	Oxybutynin Mean±SD	Placebo Mean±SD	Mean Difference	p value
VAS Change from Day1 to Day3	1.33±0.64	1.65±0.74	-0.320	0.110
VAS Change from Day1 to Day5	2.27±1.00	2.10±1.23	0.144	0.650

Efficacy analysis for frequency of micturition

Variable	Oxybutynin Mean±SD	Placebo Mean±SD	Mean Difference	p value
Frequency of Urination Change from Day1 to Day3	2.11±1.70	1.50±1.72	0.615	0.210
Frequency of Urination Change from Day1 to Day5	2.58±1.90	2.13±1.66	0.446	0.389

Efficacy analysis for Nocturia

Variable	Oxybutynin Mean±SD	Placebo Mean±SD	Mean Difference	p value
Nocturia Change from Day1 to Day3	0.416±0.50	0.19±0.49	0.2243	0.118
Nocturia Change from Day1 to Day5	0.54±0.72	0.50±0.65	0.042	0.831

Other outcomes:

There was no difference in the mean fluid intake between the two groups.

Post void residue in both the groups were comparable with mean of 30.46 ml in the study group and 33.71 ml in the placebo group. It is noteworthy that

the PVR was actually higher in the placebo group, thus ending all speculation about the theoretical possibility of retention with oxybutynin.

Adverse effects:

6 of the 24 in the oxybutynin group (25%) and 5 of the 26(20%) in the control group complained of dry mouth. However none of the patients discontinued the drug, probably because this ended by the 5th day.
None of the patients in the control or study group developed retention.

DISCUSSION

Many patients are bothered by lower urinary tract symptoms immediately or at some time after prostatectomy for benign disease. Pain only arises during urination for the first time after the removal of urinary catheter; this has been

described by some as a "sharp pin-point" pain. Many studies have addressed this issue, and the incidence of recurrent or persistent symptoms has been reported to be 5-35%. Post-prostatectomy voiding dysfunction can be divided into subjective problems, or symptoms and objective problems as determined urodynamically. When assessing symptoms, investigators have

noted that urgency and frequency occur in 45 to 75% of patients before and 20 to 35% after prostatectomy. It has been found that symptoms remaining with the greatest scores even at 3 months postoperatively are frequency, urgency and nocturia**.**

This study was aiming to answer whether oxybutynin could reduce the storage symptoms seen in the immediate post TURP period. One of the draw backs of this study was that urodynamic evaluation was not carried out. However, it is our department policy not to subject everyone undergoing TURP for pressure flow studies (PFS). PFS is reserved for specific indications viz. young males with BOO, established neurological disease and predominant storage symptoms in the IPSS. The first two categories of patients were excluded from this study, and none of the patients included had predominant storage LUTS.

Our sample size calculation was based on the Swedish study where in the difference showed in frequency was 38%. However, a closer statistical analysis of the same revealed that the previous study did not measure effective change of frequencies between the 2 groups.

Our results were different from the Swedish study, the reasons for which may be multifactorial.

Efficacy analysis did show at least an 18% benefit of the drug over placebo. The change in IPSS scores ($p=0.352$ at day 3), visual analogue score ($p=0.110$ at day 3), frequency of micturition ($p=0.389$ at day 5) and nocturia ($p=0.118$ at day 3) all showed a modest benefit. However this was not statistically significant. Of all the variables, except frequency of micturition, the maximum change between the two groups was on the 3rd day.

Whether this is of sufficient benefit to the patient, needs to be evaluated further.

The present study probably is underpowered and hence a statistically significant benefit is not evident in the results.

A larger sample size may give more information in this regard.

What is indeed novel is the simplicity of the design, and the fact that a simple, widely used drug, may alleviate bothersome symptoms.

CONCLUSION

Our hypothesis is that the frequency and urgency following TURP is partly due to the created raw surface of the resected prostatic fossa, that triggers overactivity, and that this can be reduced with anticholinergics. This is different and apart from the overactivity that is present due to BOO.

Detrusor overactivity associated with aging and benign prostatic obstruction often causes the troublesome symptoms of urgency and urgency incontinence. Persistent detrusor overactivity after transurethral resection of the prostate is the cause of more than a third of poor symptomatic outcomes following surgery.

Most of the evidence currently suggests that neurons of the urothelium at the bladder neck play a significant role in the genesis of detrusor overactivity. Anticholinergics have a definite and proven role to play, especially in the immediate post operative period. A short course of a proven anticholinergic like extended release Oxybutynin, alleviates the rather bothersome symptoms of urgency, increased frequency, and

also reduces pain in the immediate post operative period. The apprehension about possibility of retention due to anticholinergic is ill founded and none of the patients on oxybutynin had urinary retention. An improvement in frequency and nocturia was observed on the 5th day and nocturia, as also a decrease of pain during micturition, as evidenced by improvement in the visual analogue score.

From this study there is inadequate evidence to suggest routine use of anticholinergics after TURP, to reduce symptoms of frequency and urgency in the immediate postoperative period.

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